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ZAHTEVA ZA PODELITEV PATENTA

1. Naslov za obveščanje:

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Potrdilo o prejemu prijave
(izpolni urad)

Datum vložitve prijave: 31. 3. 2004

Številka prijave: P- 200400101

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2. Prijavitelj (priimek, ime in naslov, za pravne osebe firma in sedež):

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Registrska številka: 161

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6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

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Prejeto dne: 31 -03- 2004	Osebna oddaja: ☐
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____KOŠAK Alenka_____
Priimek in ime ter podpis prijavitelja (zastopnika

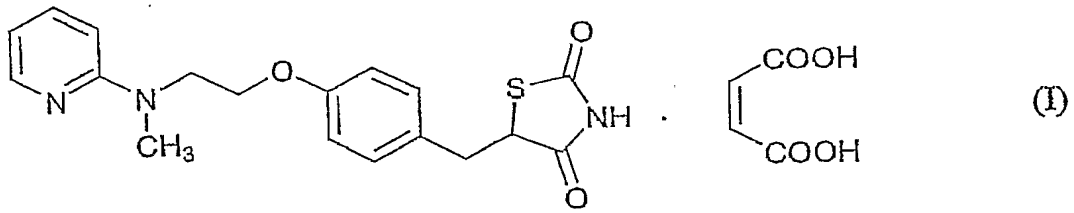
Obrazec SIPO P-1

Novel co-precipitate

Field of the invention

(Int. Cl.: **C07 D 417/12**, A61 K 31/425, A61 K 31/44)

The present invention relates to novel stable amorphous form of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate and its stereo-isomers having formula (I),(hereinafter referred as rosiglitazone maleate), to novel co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier, to a novel pharmaceutical composition comprising said novel co-precipitate, to a process for the preparation of said novel co-precipitate and to its use in medicine. The novel co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier is useful for the treatment and / or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof. Diabetes mellitus preferably means Type II diabetes mellitus.



(I)

Technical problem

There is a constant need for preparing stable pharmaceutical form comprising rosiglitazone maleate which would be particularly stable for bulk preparation and handling.

Prior art

Rosiglitazone is a well-known active compound, described in EP 306228 A1 also in a tautomeric form and / or its pharmaceutically acceptable salt thereof, and / or a pharmaceutically acceptable solvate thereof, useful for the treatment and / or prophylaxis of hyperglycaemia, hyperlipidaemia or hypertension.

PCT application, publication number WO 94/05659, discloses certain thiazolidinedione derivatives or a tautomeric form thereof and / or a pharmaceutically acceptable solvate therfeof, including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleic acid salt (rosiglitazone maleate) as preferred compound, which is active compound in commercial drug Avandia®. Rosiglitazone maleate is significantly more soluble in water than the corresponding free base and show also good stability in the solid form.

PCT applications, publ. numbers WO 99/31093, WO 99/31094 and WO 99/31095 each disclose novel hydrates of rosiglitazone maleate, a process for the preparation of such a compound, a pharmaceutical composition containg such a compound and the use of such a composition for the treatment of diabetes mellitus.

PCT applications, publ. numbers WO 00/64892, WO 00/64893 and WO 00/64896 describe novel polymorphs of rosiglitazone maleate, a process for preparing such polymorphs, a pharmaceutical composition containing such polymorphs and the use of such polymorphs for the treatment of diabetes mellitus.

PCT application, publ. number WO 02/26737, discloses novel polymorphic / pseudopolymorphic forms I – IV of rosiglitazone maleate, a pharmaceutical composition comprising the novel polymorphic form or their mixture and a pharmaceutically acceptable carrier.

Description of the invention

The present invention relates to a novel stable amorphous form of rosiglitazone maleate and its stereomers and to a novel co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier which is particularly stable for bulk preparation and handling.

A pharmaceutically acceptable carrier may be selected from the group consisting of polyvinylpyrrolidone, silicon dioxide, mannitol and a cyclodextrine. The cyclodextrine may be any member of broad group of natural α, β and gamma cyclodextrines or semisynthetic cyclodextrines, e.g. ß-hydroxypropyl cyclodextrine.

A further aspect of the present invention is a process for the preparation of co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier, which comprises the steps of:

a) dissolving rosiglitazone maleate in an aqueous solution of organic solvent,
b adding pharmaceutically acceptable carrier,
c) spray-drying the obtained solution.

During the process starting crystalline rosiglitazone maleate transforms to amorphous rosiglitazone maleate and forms novel co-precipitate of the present invention.

Starting crystalline rosiglitazone maleate for said process may be prepared according to the teaching of WO 94/05659.

The organic solvent may be selected from the group consisting of ethanol and acetone, in the range from about 9 : 1 to about 7 : 3 V / V of organic solvent to water.

The amorphous form of rosiglitazone maleate in the novel co-precipitate with pharmaceutically acceptable carrier was detected by X-ray powder diffraction diagrams, measured using a AXS-Bruker D-8 diffractometer (Cu-radiation, Bragg-Brentano Optics, 40 kV, 40 mA, steps 0.01°, time 2 seconds, cut-off: 40°, standard sample carrier).

X-ray powder diffraction analyses were additionally repeated twice for each sample in order to test the stability under ambient conditions and X-ray radiation. No changes in X-ray powder diffraction patterns were observed. Analyses were carried out by means of software DiffracPlus.

All obtained analyses of novel co-precipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone, silicon dioxide, mannitol or gamma-cyclodextrin show X-ray amorphous pattern. The structures of amorphous pattern is a little different what may depend on pharmaceutically acceptable carrier used.

Novel co-precipitate of amorphous rosiglitazone maleate with mannitol show crystalline pattern and one amorphous background. The pattern is not in accord with starting crystalline mannitol and also not in accord with starting crystalline rosiglitazone maleate. The reason for this may be the transformation of mannitol into the mixture of α-D-mannitol and δ (delta)-D-mannitol during the process and the remaining background is a guidance that amorphous rosiglitazone maleate is present.

A further aspect of the present invention are novel stable pharmaceutical compositions, e.g. tablets, capsules, parenteral dosage forms, comprising co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier and other suitable excipients.

A still further aspect of the present invention relates to novel co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier for use in the treatment and / or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The following examples illustrate the invention but do not limit it in any way.

Example 1

Rosiglitazone maleate (5.0 g) is dissolved in 150 ml of ethanol (96%) and water (9 : 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Polyvidone K30 [polyvinylpyrrolidone] (10.0 g) is added and stirred again until a solution is obtained. The obtained solution is spray-dried on a mini spray-dryer (Büchi 190). Co-precipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone presented as X-ray powder diffraction pattern on Fig. 4 is obtained.

Starting rosiglitazone maleate is crystalline compound presented as X-ray diffraction pattern on Fig. 2.

Polyvidon K30 is amorphous compound presented as X-ray powder diffraction pattern on Fig. 16.

Example 2

Rosiglitazone maleate (5.0 g) is dissolved in 150 ml acetone and water (7 : 3, V / V) and stirred until a clear solution is obtained. To the obtained solution Polyvidone [polyvinylpyrrolidone] (10.0 g) is added and stirred again until a solution is obtained. The obtained solution is spray-dried on a mini spray-dryer (Büchi 190). Co-precipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone is obtained.

Example 3

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of ethanol (96%) and water (9: 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Polyvidone [polyvinylpyrrolidone] (20.0 g) is added and stirred again until a solution is obtained. The obtained solution is spray-dried on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone is obtained.

Example 4

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of acetone and water (7 : 3,V / V) and stirred until a clear solution is obtained. To the obtained solution Polyvidone [polyvinylpyrrolidone] (20.0 g) is added and stirred again until a solution is obtained. The solution is spray-dried on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone presented on Fig. 5 is obtained.

Example 5

Rosiglitazone maleate (5.0 g) is dissolved in 150 ml of ethanol (96%) and water (9 : 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Polyvidone [polyvinylpyrrolidone] (5.0 g) is added and stirred again until a solution is obtained. The obtained solution is spray-dried on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone presented on Fig. 6 is obtained.

Example 6

Rosiglitazone maleate (5.0 g) is dissolved in 150 ml of acetone and water (7 : 3, V / V) and stirred until a clear solution is obtained. To the obtained solution Polyvidone [polyvinylpyrrolidone] (5.0 g) is added and stirred again until a solution is obtained. The obtained solution is spray-dried on a mini spray-dryer (Büchi). Co-precipitate of

amorphous rosiglitazone maleate with polyvinylpyrrolidone presented on Fig. 7 is obtained.

Example 7

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of ethanol (96%) and water (1 : 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Mannit [mannitol] (10.0 g) is added and stirred again until a solution is obtained. The obtained solution is spray-dried on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with mannitol presented as X-ray powder diffraction pattern on Fig. 8 is obtained. X-ray diffraction pattern on Fig. 14 shows that in the remaining background amorphous rosiglitazone maleate is present.

Mannit (Merck) is crystalline compound presented as X-ray diffraction pattern on Fig. 15.

Example 8

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of acetone and water (1 : 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Mannit [mannitol] (10.0 g) is added and stirred again until a turbid solution is obtained. The obtained turbid solution is spray-dried on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with mannitol presented as X-ray powder diffraction pattern on Fig. 9 is obtained.

Example 9

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of acetone and water (9 : 1, V / V) and stirred until a clear soilution is obtained. To the obtained solution Aerosil 200 [silicon dioxide] (10.0 g) is added and stirred for 10 minutes. The obtained suspension is spray-dried with stirring on a mini spray-dryer (Büchi 190). Co-

precipitate of amorphous rosiglitazone maleate with silicon dioxide presented as X-ray powder diffraction pattern on Fig. 10 is obtained.

Aerosil 200 is amorphous compound presented as X-ray powder diffraction pattern on Fig. 1.

Example 10

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of acetone and water (9 : 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Aerosil 200 [silicon dioxide] (5.0 g) is added and stirred for 10 minutes. The obtained suspension is spray-dried with stirring on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with silicon dioxide is obtained.

Example 11

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of ethanol (96%) and water (9 : 1, V / V) and stirred until a clear solutiuon is obtained. To the obtained solution Aerosil 200 [silicon dioxide] (5.0 g) is added and stirred for 10 minutes. The obtained suspension is spray-dried with stirring on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with silicon dioxide presented as X-ray diffraction pattern on Fig. 11 is obtained.

Example 12

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of ethanol (96%) and water (9 : 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Aerosil 200 [silicon dioxide] (10.0 g) is added and stirred for 10 minutes. The obtained suspension is spray-dried with stirring on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with silicon dioxide is obtained.

Example 13

Rosiglitazon maleate (5.0 g) is dissolved in 300 ml of acetone and water (9 : 1, V / V) and stirred until a clear solution is obtained. To the obtained solution Syloid [amorphous silicon dioxide] (20.0 g) is added for 10 minutes. The obtained suspension is spray-dried with stirring on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with silicon dioxide presented as X-ray powder diffraction pattern on Fig. 12 is obtained.

Syloid is amorphous compound presented as X-ray powder diffraction pattern on Fig. 17.

Example 14

Rosiglitazone maleate (5.0 g) is dissolved in 300 ml of ethanol (96%) and water (9 : 1, V / V) and stirred until a clear solution is obtained, To the obtained solution Syloid [amorphous silicon dioxide] (20.0 g) is added and stirred for 10 minutes. The obtained suspension is spray-dried with stirring on a mini spray-dryer (Büchi). Co-precipitate of amorphous rosiglitazone maleate with silicon dioxide is obtained.

Example 15

Rosiglitazone maleate (5.0 g) is dissolved in 150 ml of ethanol (96%) and 50 ml water and stirred until a clear solution is obtained. To the obtained solution a solution of Cavamax W8 [gamma-Cyclodextrin] (10.0 g) in 100 ml water is added and stirred again for 10 minutes. The obtained solution is spray-dried on a mini spray-drier (Büchi). Co-precipitate of amorphous rosiglitazone maleate with gamma cyclodextrin as presented on Fig. 13 Is obtained.

Cavamax W8 is crystalline compound presented as X-ray powder diffraction pattern on Fig. 3.

Claims

1. An amorphous form of rosiglitazone maleate, and its stereoisomers.

2. A co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier.

3. A co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier according to claim 2, wherein the carrier selected from the group consisting of polyvinylpyrrolidone, silicium dioxide, mannitol and cyclodextrin.

4. A co-precipitate according to claim 2, wherein it is the co-precipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone.

5. A co-precipitate according to claim 2, wherein it is the co-precipitate of amorphous rosiglitazone maleate with silicon dioxide.

6. A co-precipitate according to claim 2, wherein it is the co-precipitate of amorphous rosiglitazone maleate with mannitol

7. A co-precipitate according to claim 2, wherein it is the co-precipitate of amorphous rosiglitazone maleate with gamma-ciclodextrin.

8. A process for the preparation of co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier, which comprises the steps of:
   a) dissolving rosiglitazone maleate in an aqueous solution of organic solvent,
   b) adding pharmaceutically acceptable carrier,
   c) spray-drying the obtained solution.

9. A process according to claim 8, wherein the pharmaceutically acceptable carrier is selected from the group consisting of polyvinylpyrrolidone, silicon dioxide, mannitol and cyclodextrin.

10. A process according to claim 8, wherein the organic solvent is selected from the group consisting of ethanol and acetone.

11. A process according to claims 8 to 10, wherein the range of organic solvent and water is from about 9 : 1 to about 7 : 3 (V / V)

12. A pharmaceutical composition comprising a therapeutically effective amount of co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier and other excipients.

13. A co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier according to claims 1 to 7, for use in the treatment and / or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

14. The use of co-precipitate of amorphous rosiglitazone with pharmaceutically acceptable carrier according to claims 1 to 7, for the manufacture of a medicament for the treatment and / or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Abstract

A novel amorphous form of rosiglitazone maleate, a novel co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier, e.g. polyvinylpyrolidone, mannitol, cyclodextrin or silicon dioxide, a process for the preparation of said novel co-precipitate and the use of novel co-precipitate of amorphous rosiglitazone with pharmaceutically acceptable carrier in the treatment and / or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, are disclosed.

Novel co-precipitate of amorphous rosiglitazone maleate with pharmaceutically acceptable carrier has greater stability than rosiglitazone maleate alone and would be particularly suitable for bulk preparation and handling.

Fig 1/17

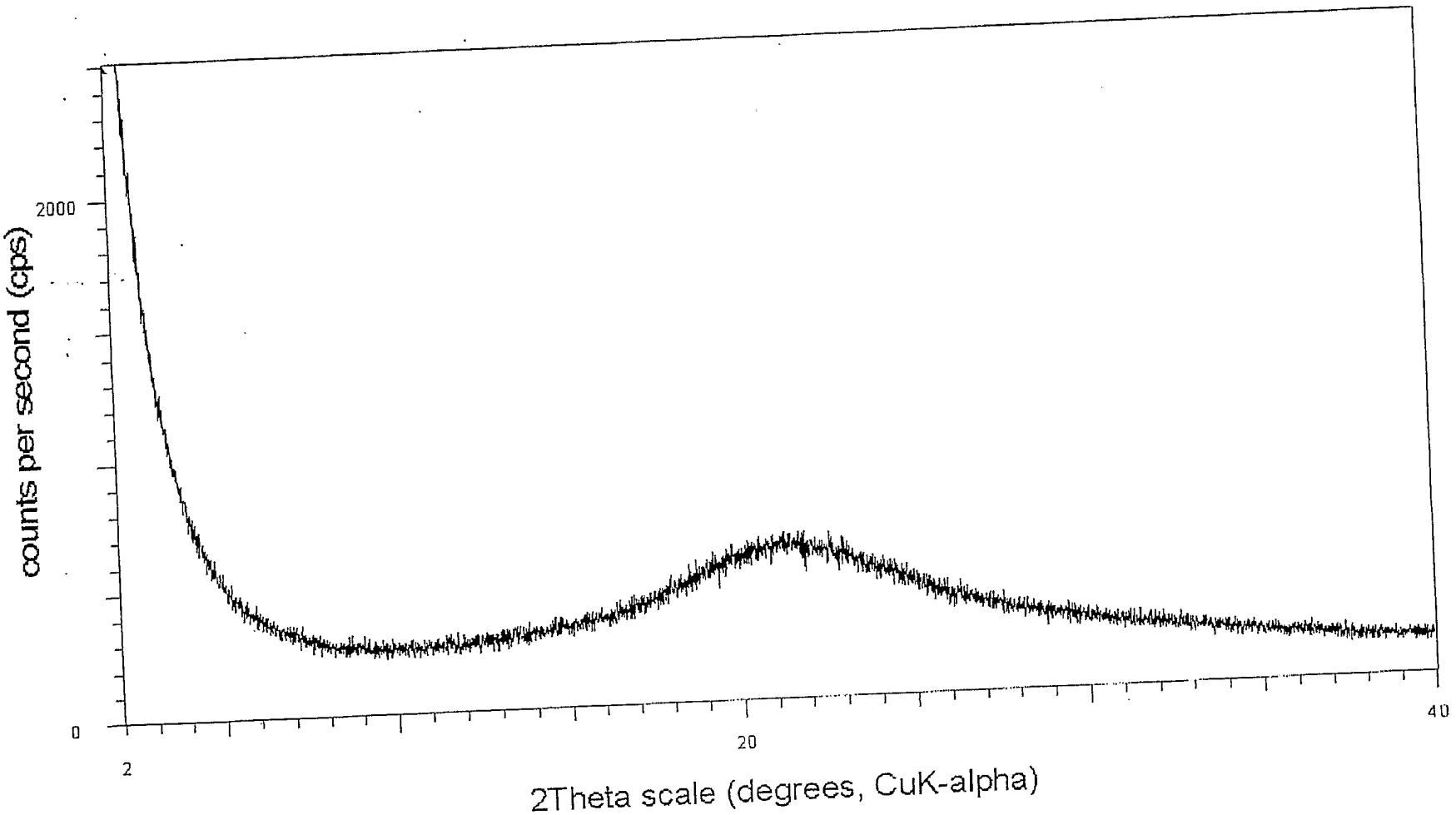

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Fig 2/17

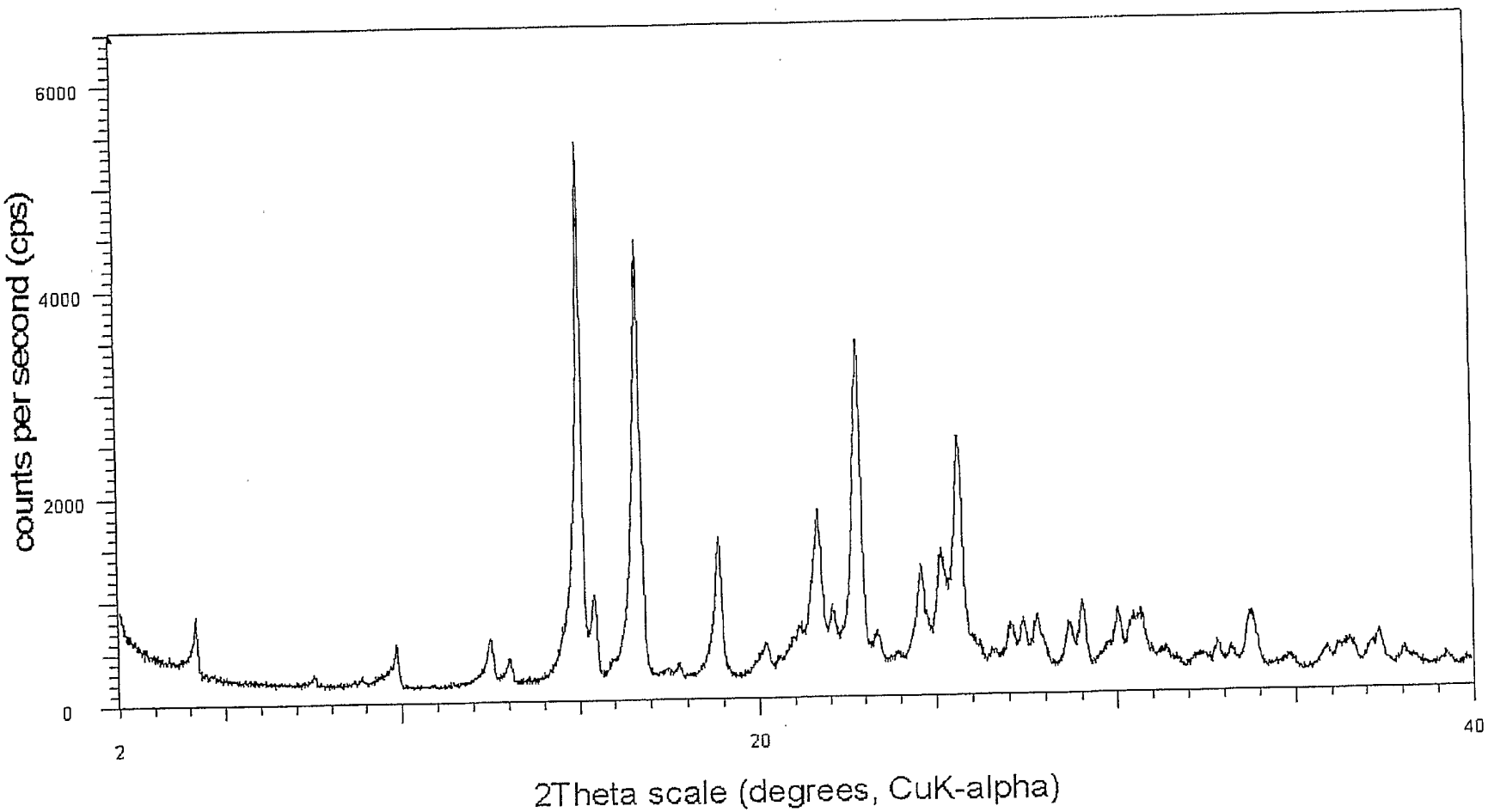
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Fig 3/17

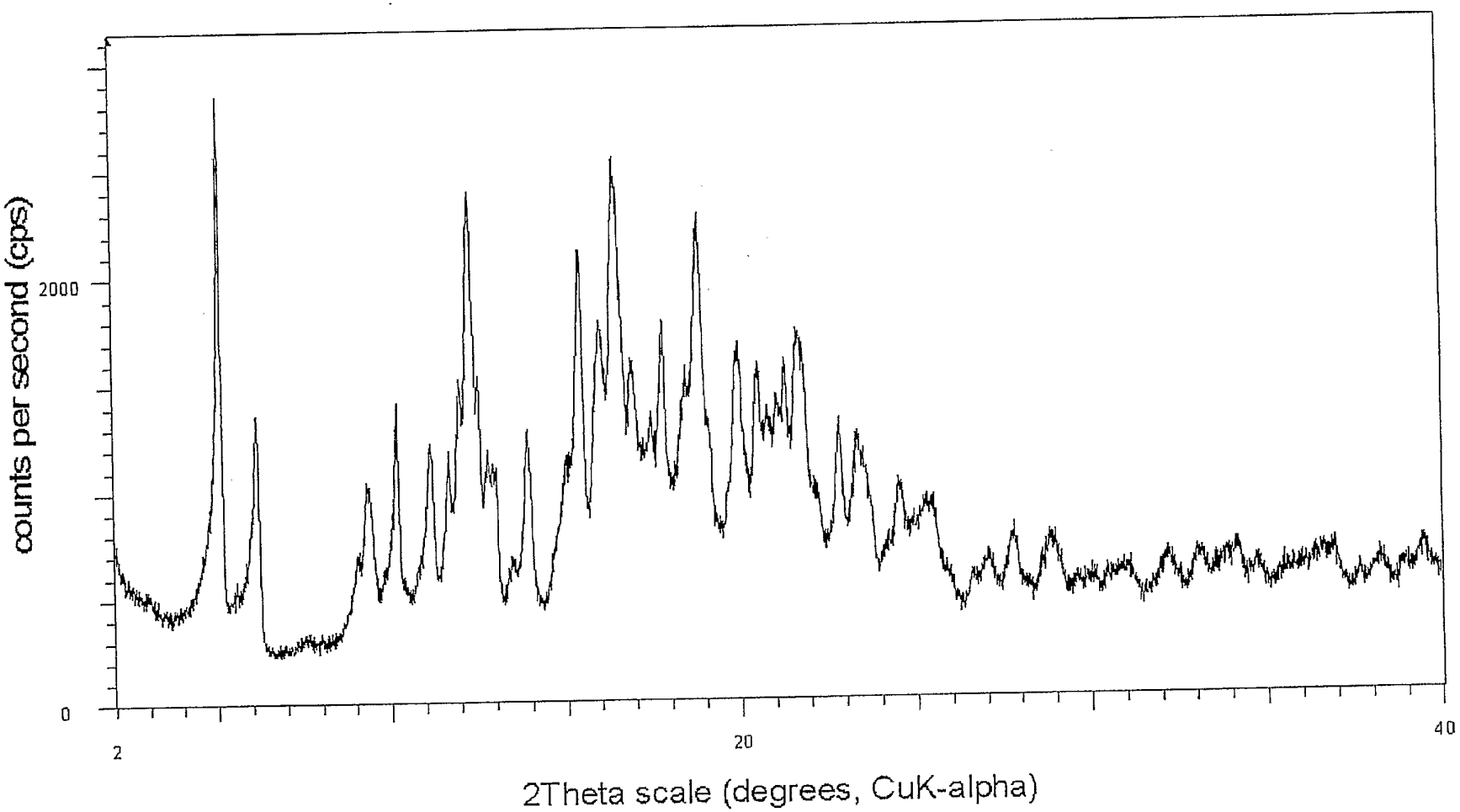
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Fig 4/17

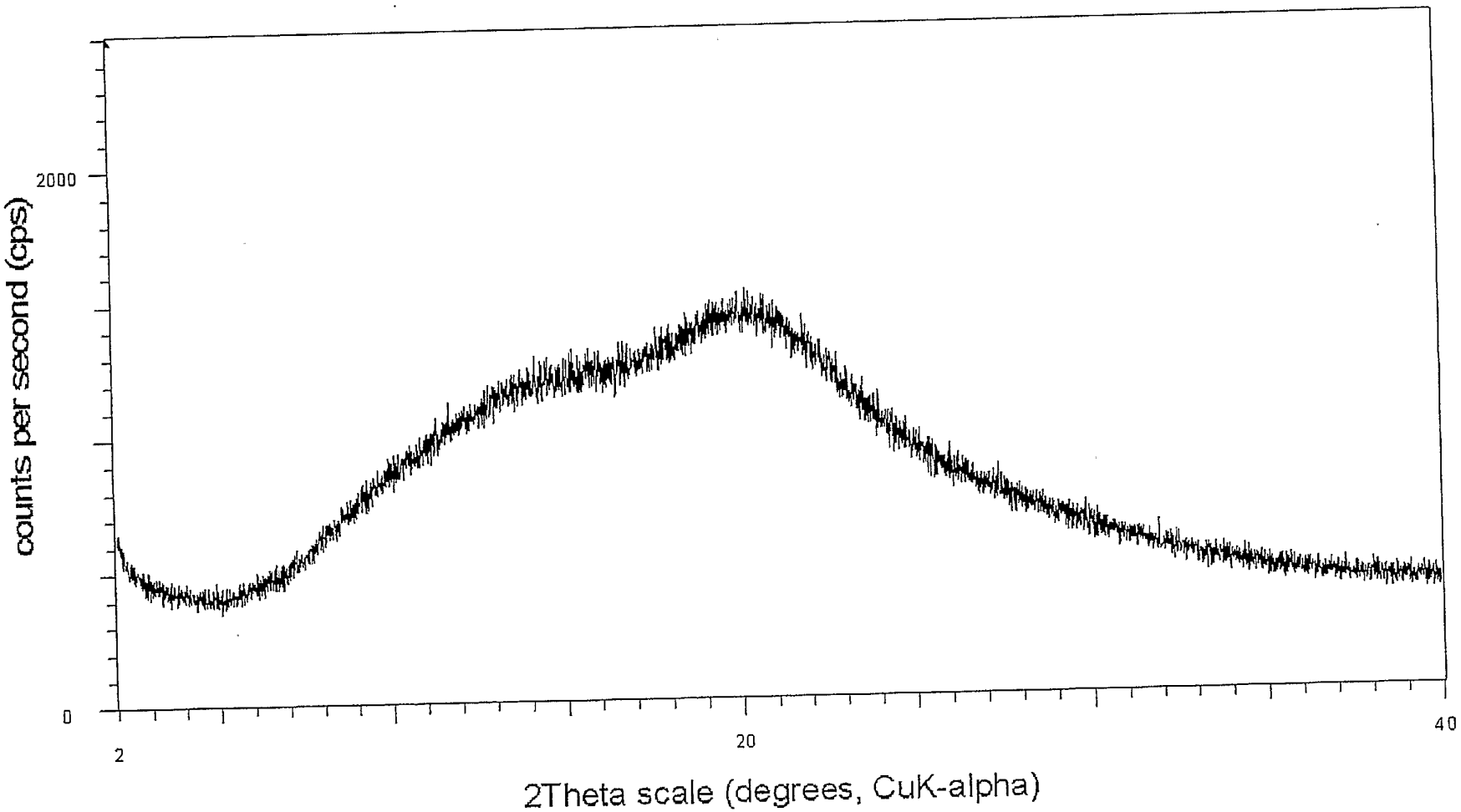
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Fig 5/17

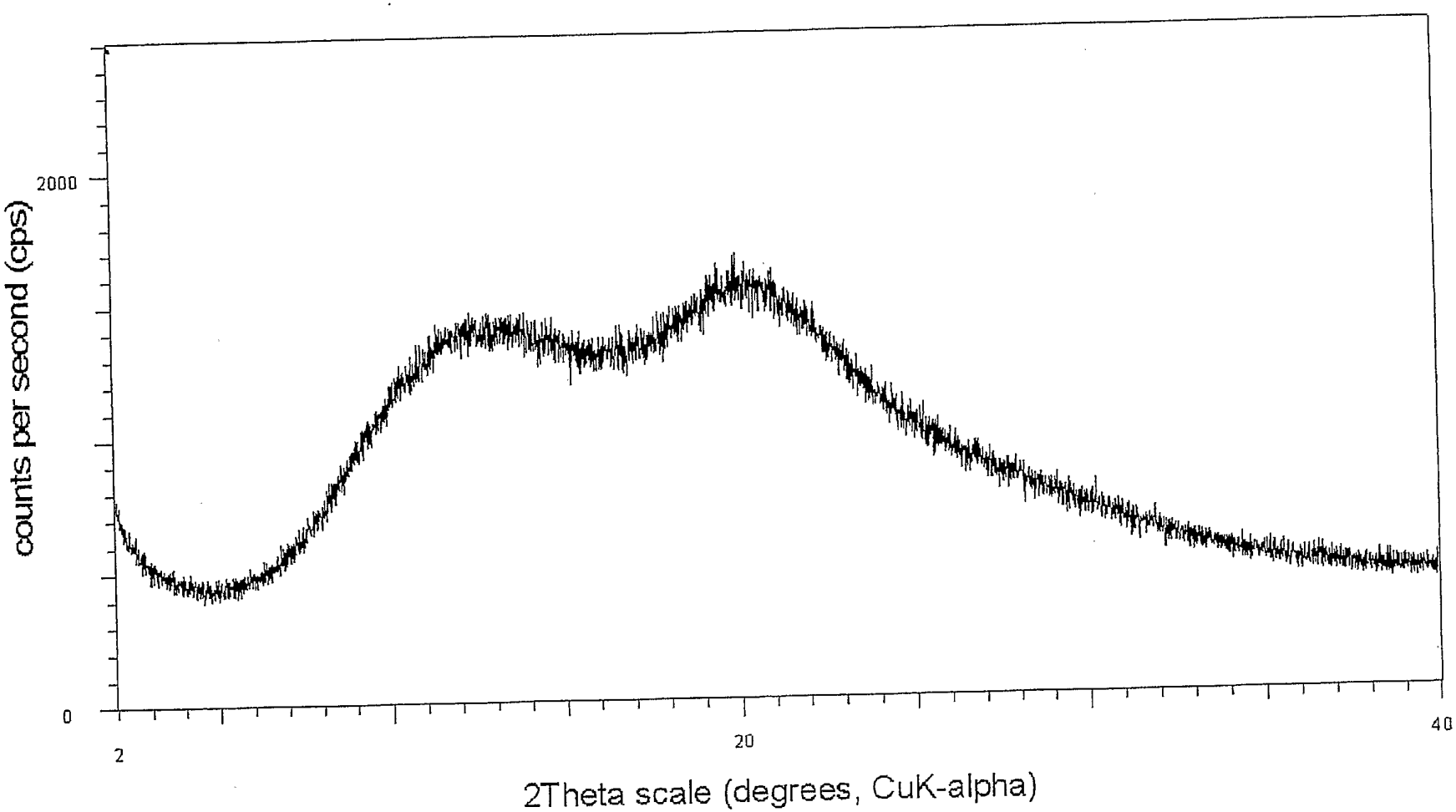
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Fig 6/17

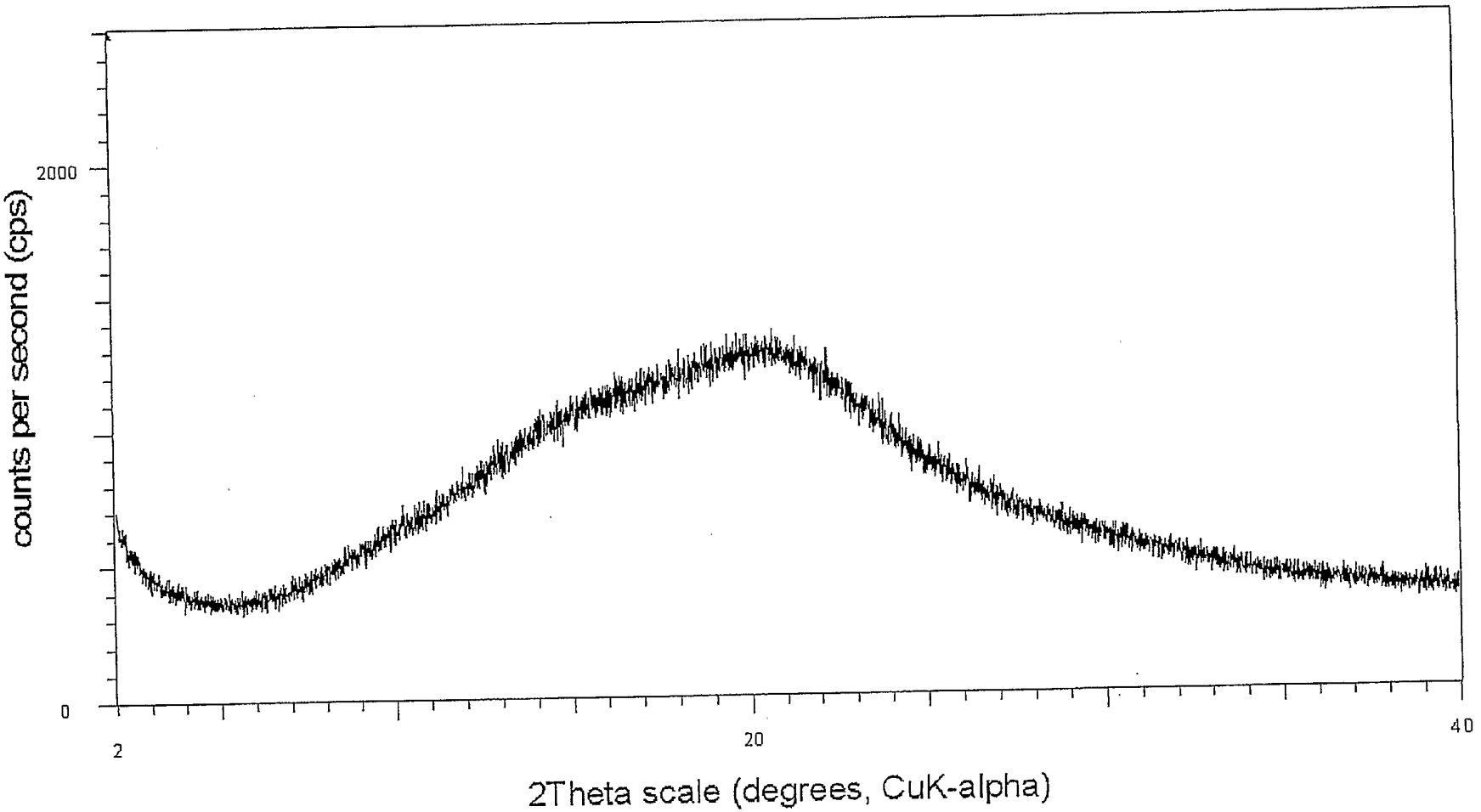
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Fig 7/17

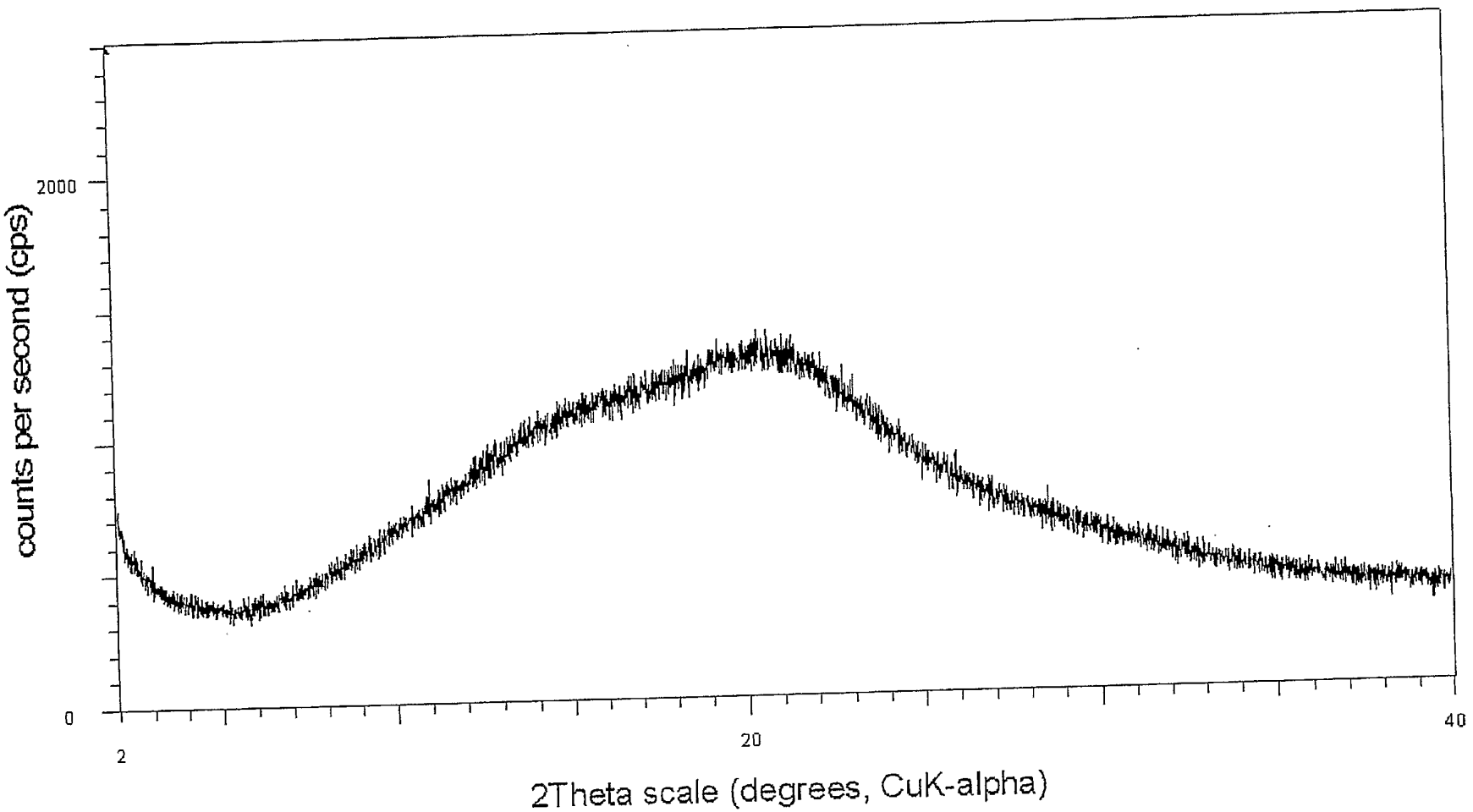
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Fig 8/17

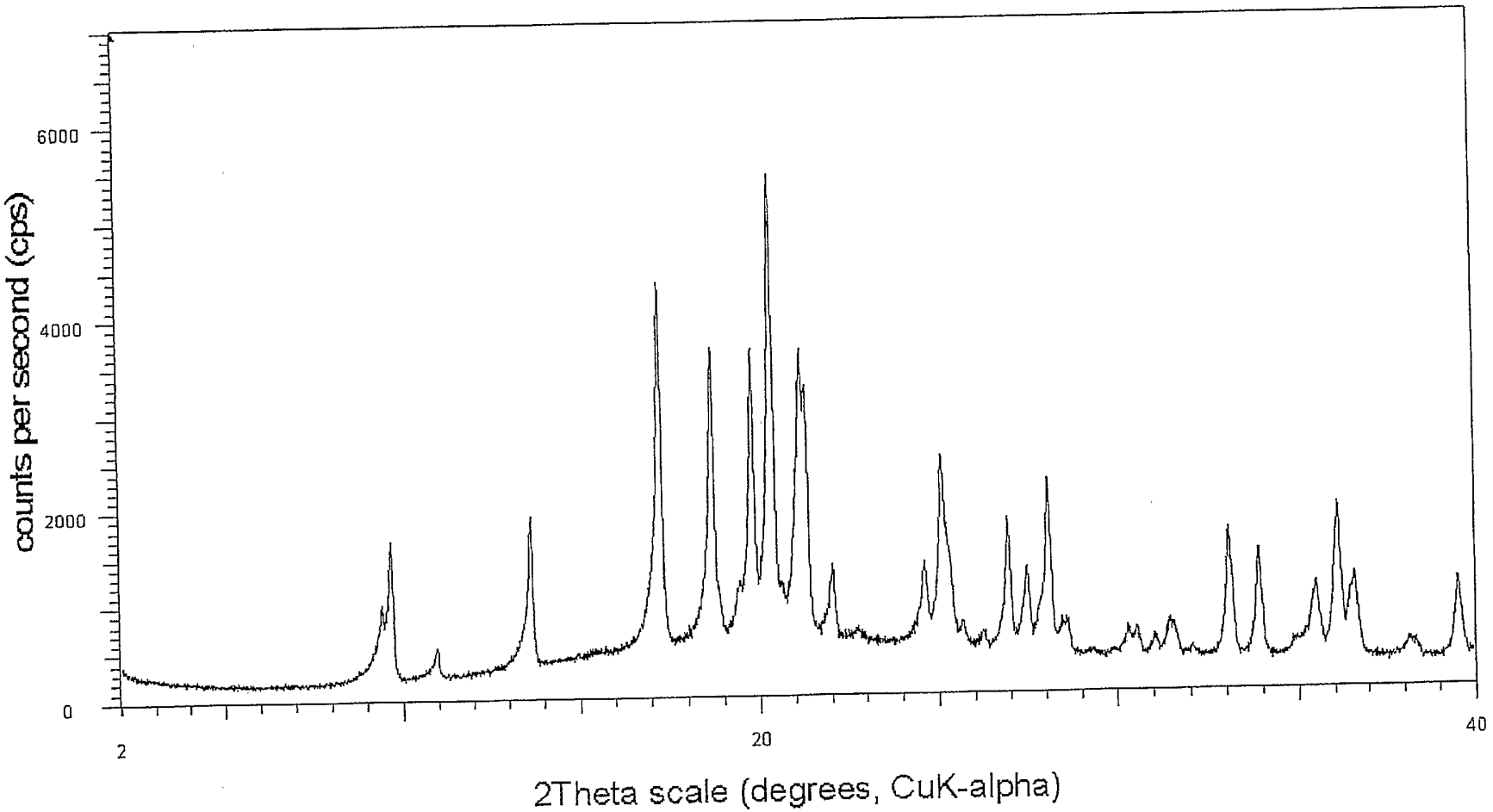
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Fig 9/17

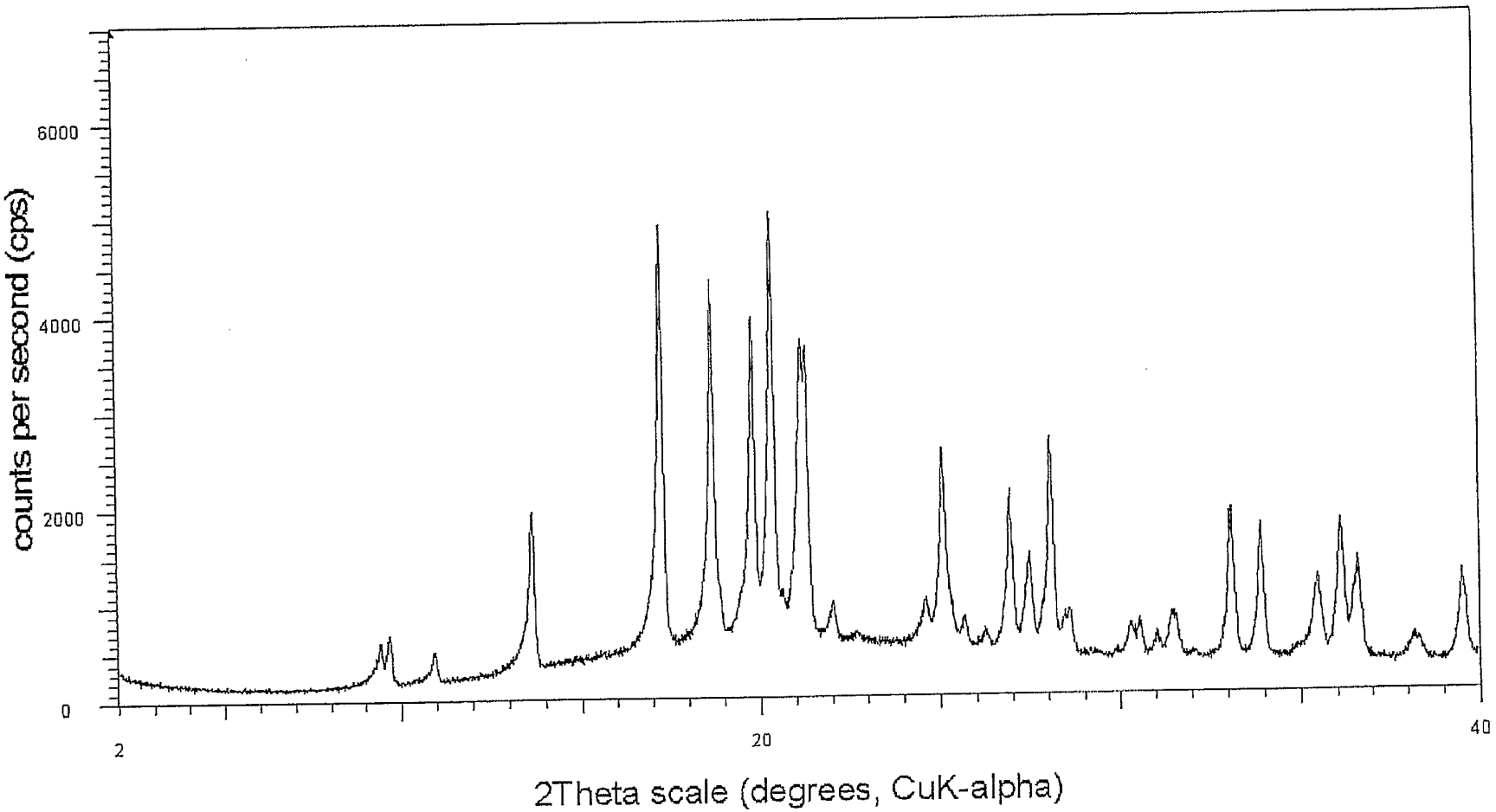
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Fig 10/17

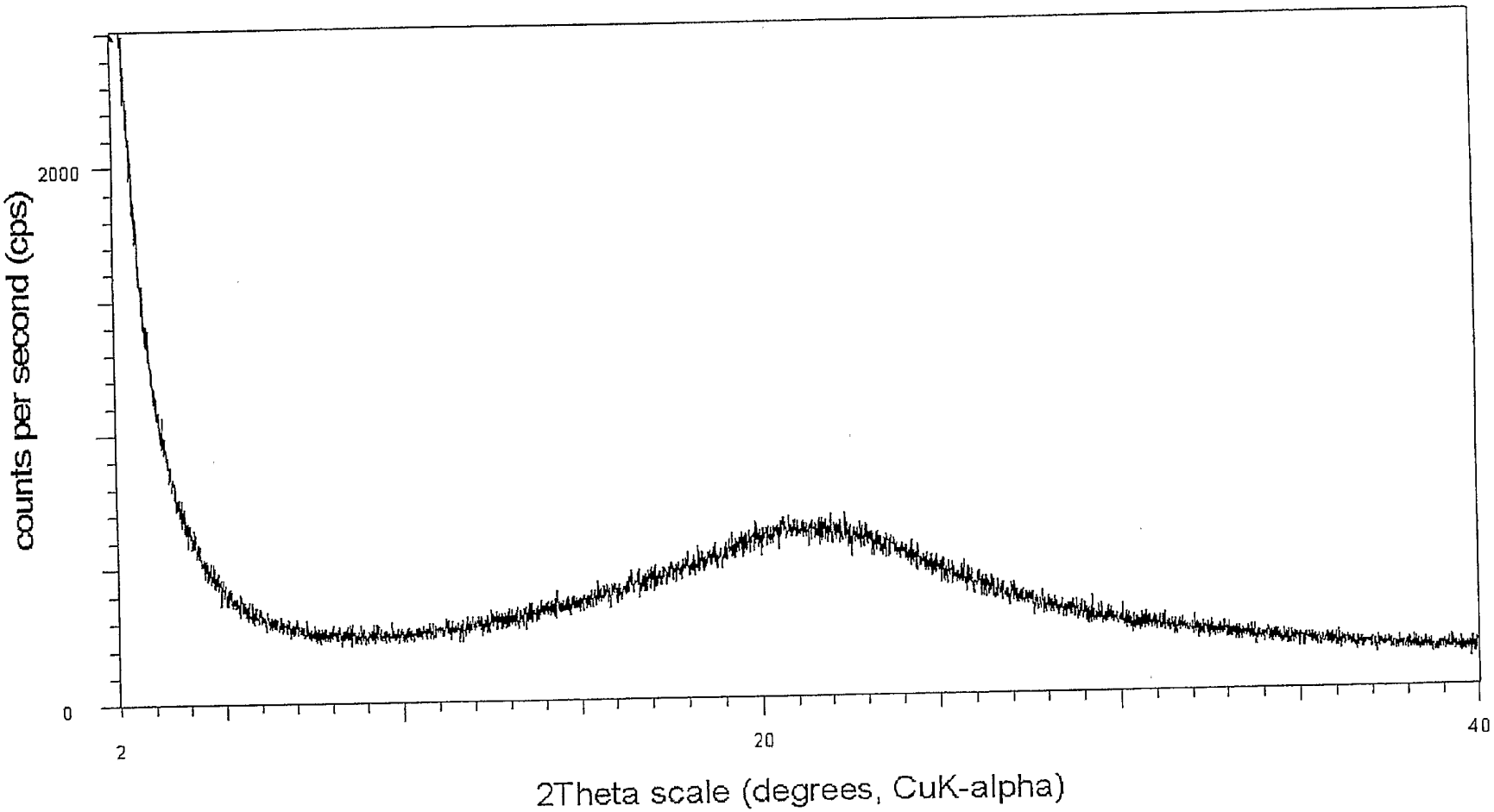
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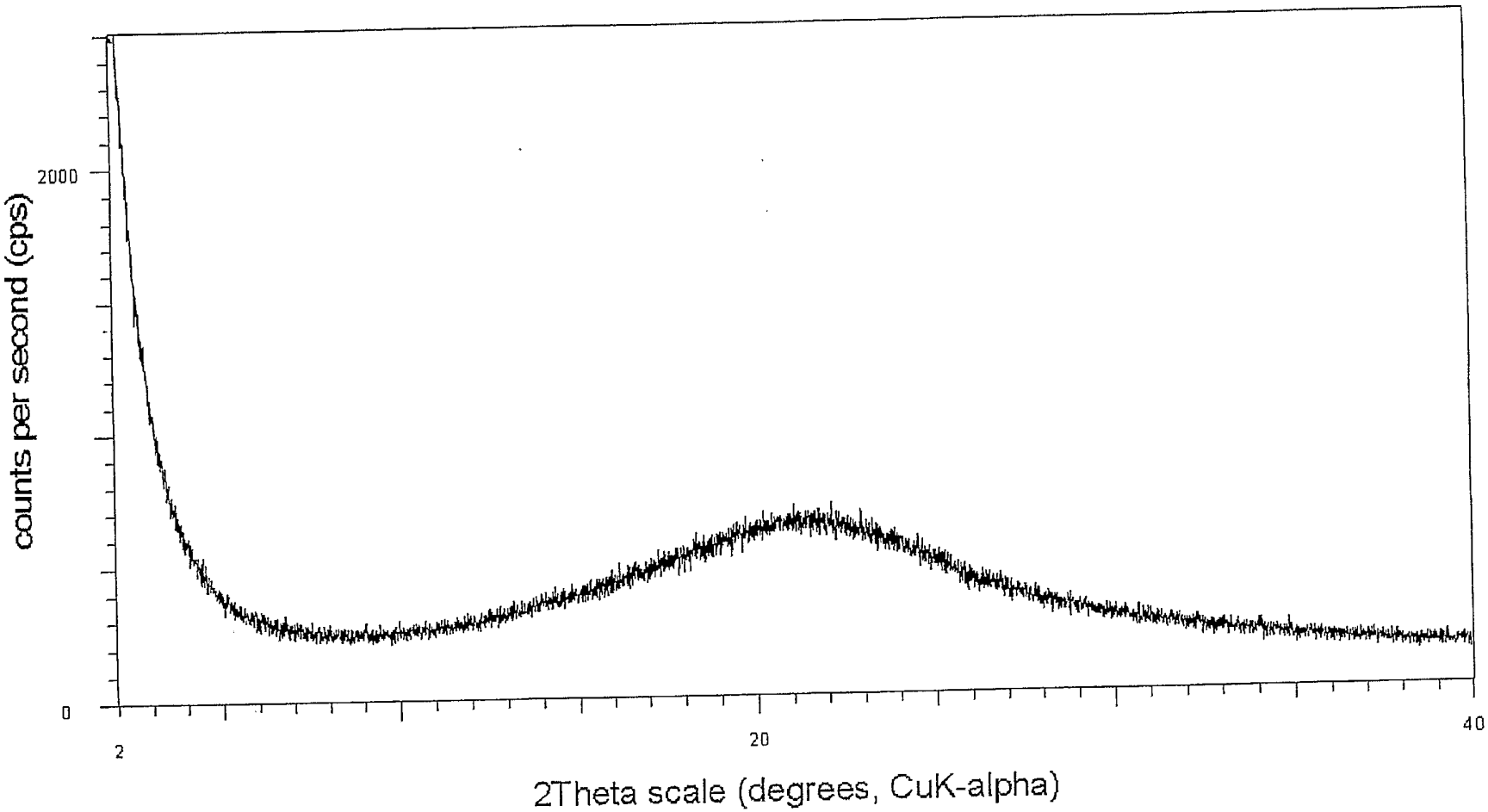
Fig 11/17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2Theta scale (degrees, CuK-alpha)

Fig 12/17

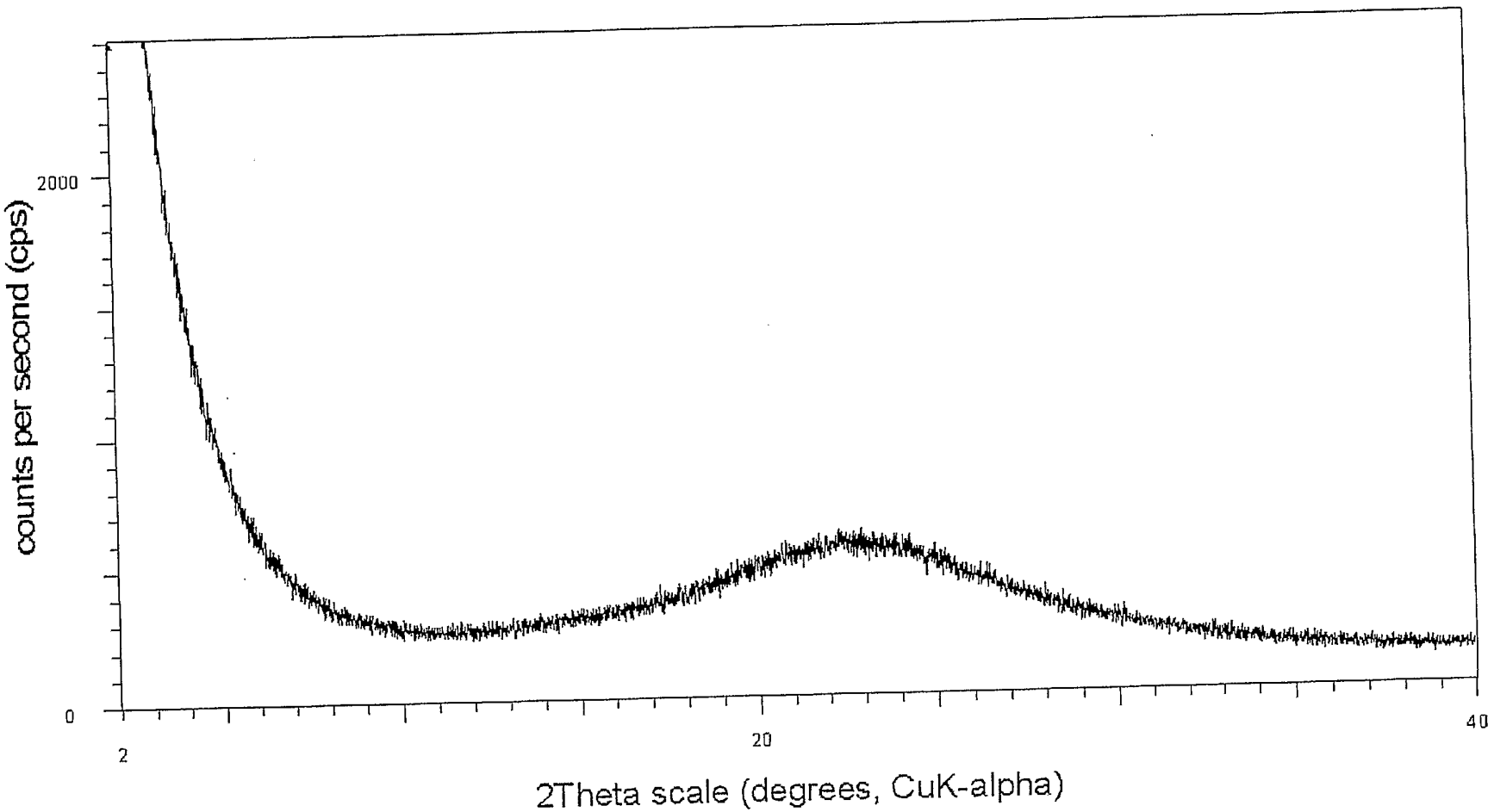

counts per second (cps)
2000
0
2
20
40
2Theta scale (degrees, CuK-alpha)

Fig 13/17

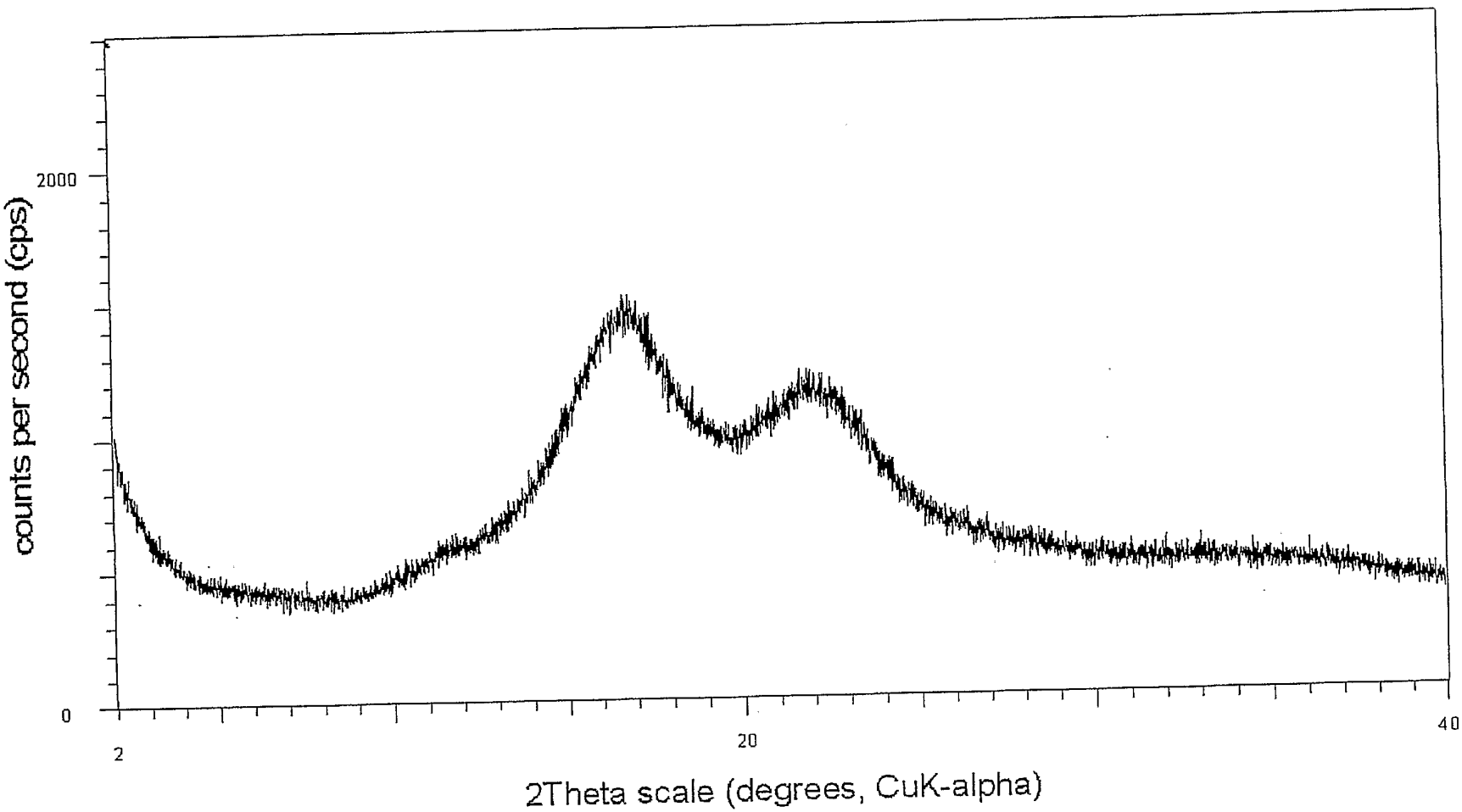

counts per second (cps)
2000
0
2
20
40
2Theta scale (degrees, CuK-alpha)

Fig 14/17

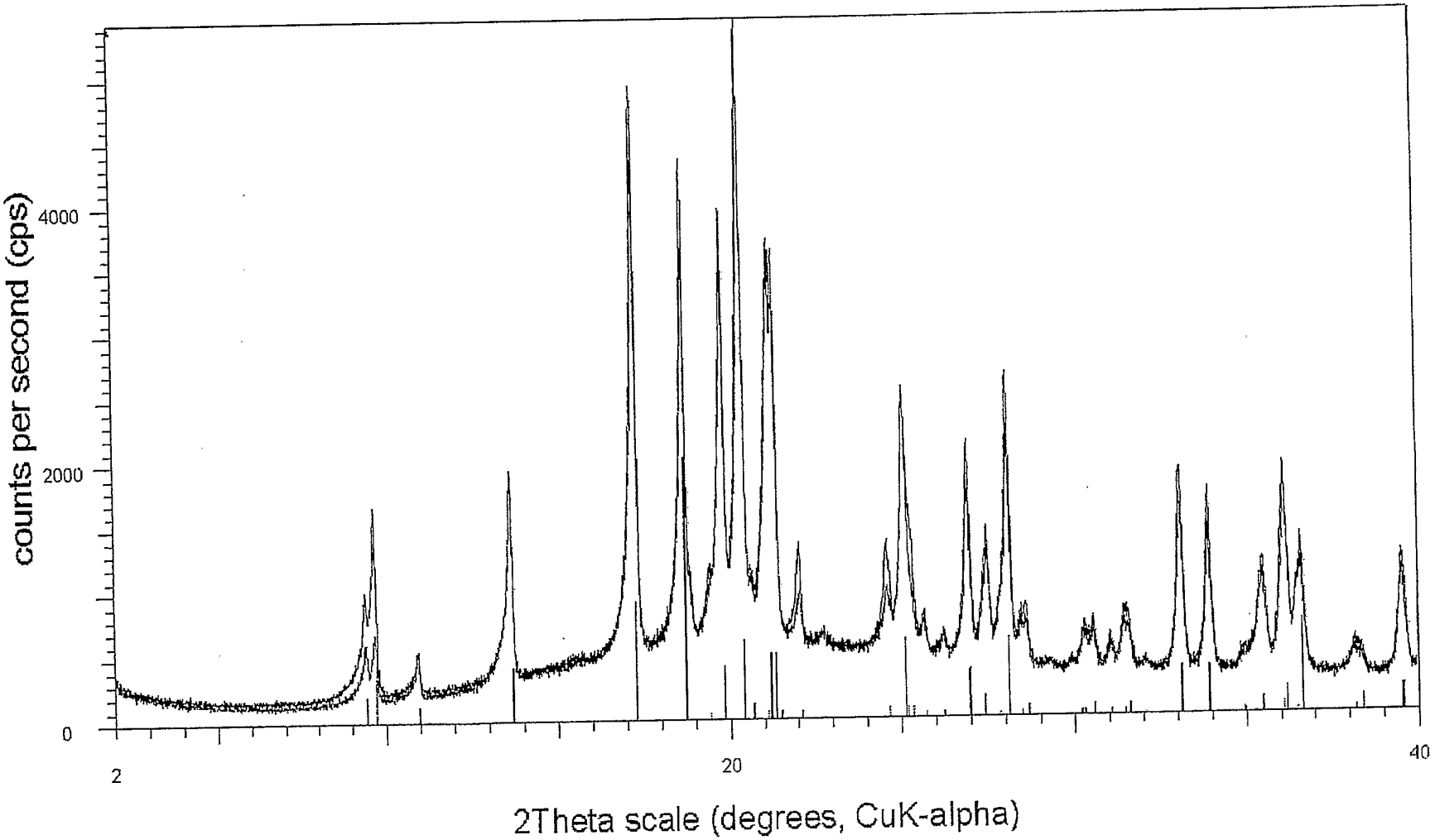

counts per second (cps)
4000
2000
0
2
20
40
2Theta scale (degrees, CuK-alpha)

Fig 15/17

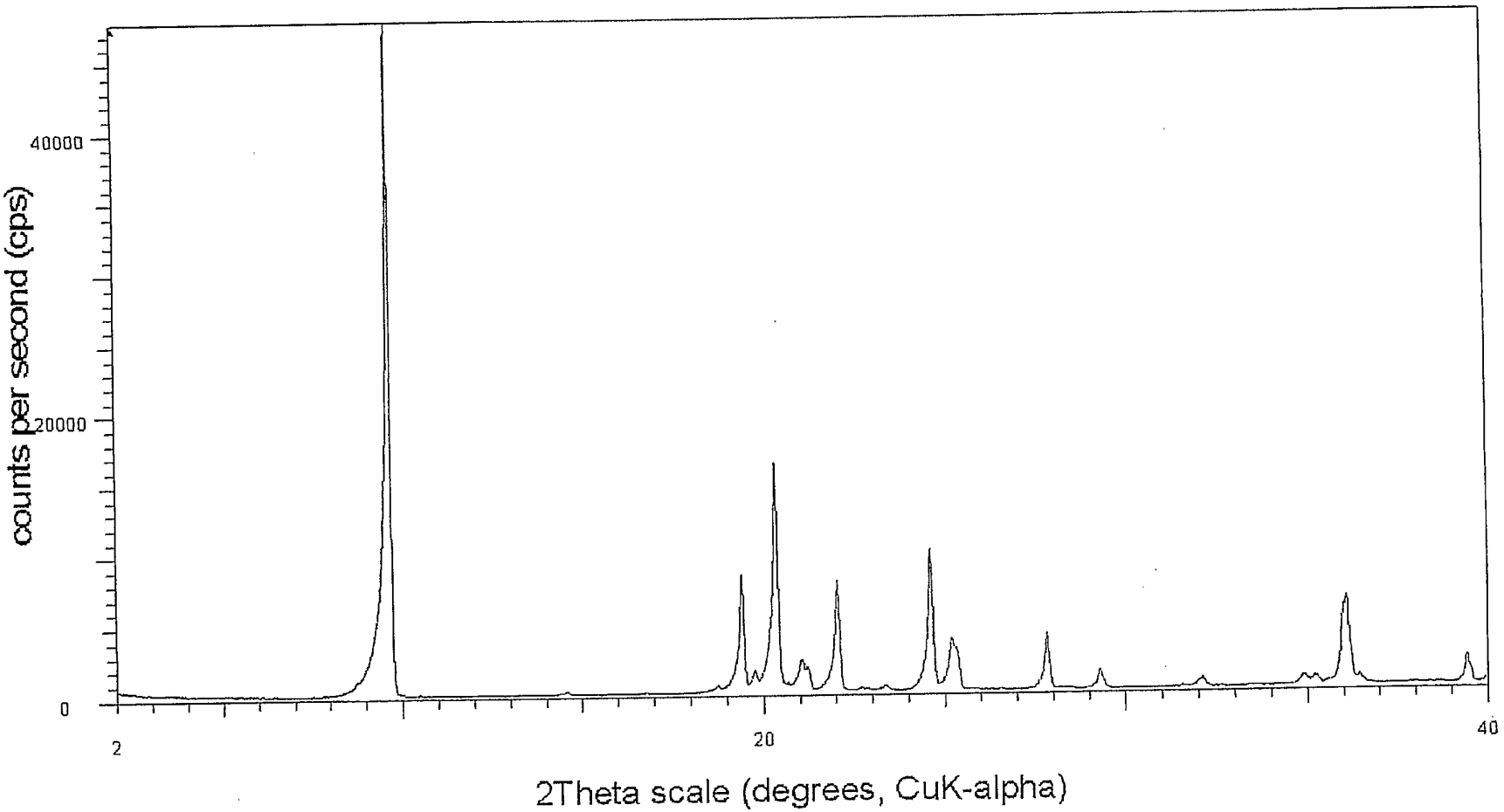

counts per second (cps)
40000
20000
0
2
20
40
2Theta scale (degrees, CuK-alpha)

Fig 16/17

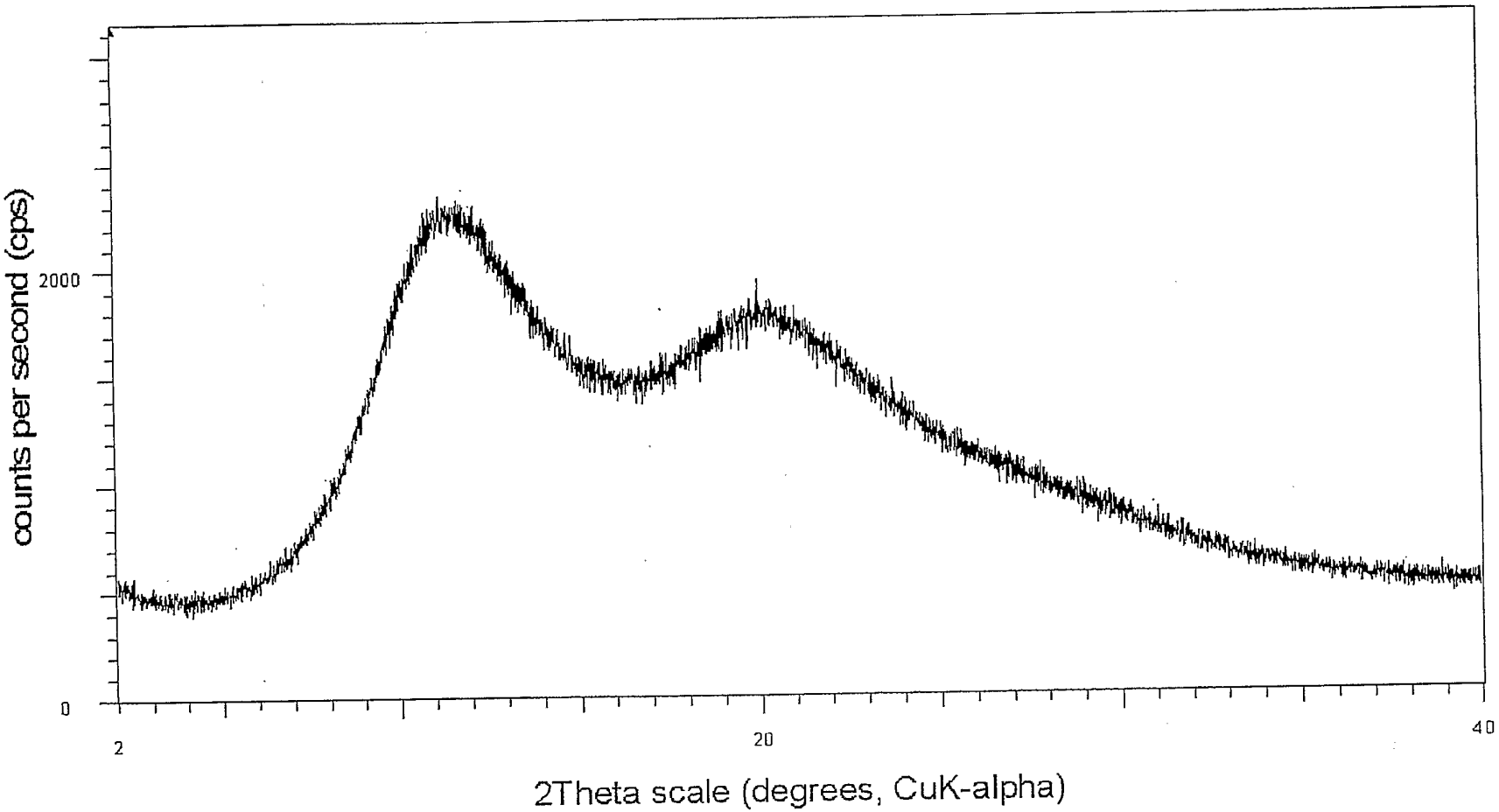
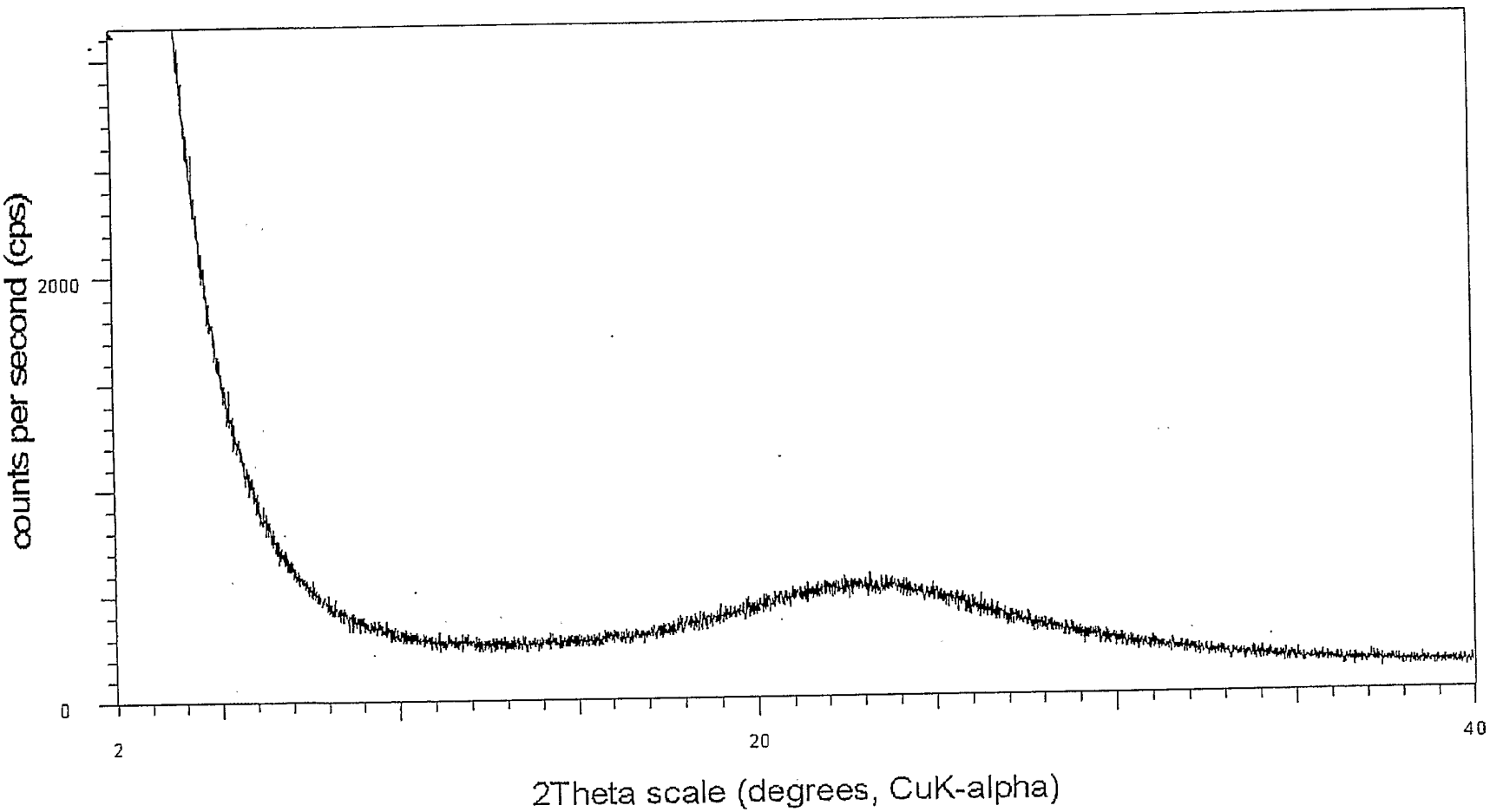

counts per second (cps)
2000
0
2
20
40
2Theta scale (degrees, CuK-alpha)

Fig 17/17


counts per second (cps)
2000
0
2
20
40
2Theta scale (degrees, CuK-alpha)